These amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter or agreement with the Examiner's position. In accordance with the requirements of 37 C.F.R. § 1.121, a marked up version showing the changes to the claims, is attached herewith as Appendix A. For the Examiner's convenience, a complete claim set of the currently pending claims is also submitted herewith as Appendix B.

REMARKS

Status of the Claims.

Claims 1-3, 4, 10, 12-15, 17, 21, 40-45, and 71-73 are pending with entry of this amendment, claims 4, 6-8, 11, 16, 18-20, 22-39, and 46-70 being cancelled and no claims being added herein. Claims 1, 2, 3, 5, 9, 10, 12, 13, 14, 15, 17, 72, and 73 are amended herein. These amendments introduce no new matter. Support is replete throughout the specification (*e.g.*, in the claims as originally filed).

Election/Restriction.

Pursuant to a restriction requirement made final, Applicants cancel claims 6-8, 22, 24-39, and 46-70 with entry of this amendment. Please note, however, that Applicants reserve the right to file subsequent applications claiming the canceled subject matter and the claim cancellations should not be construed as abandonment or agreement with the Examiner's position in the Office Action.

Priority.

Applicants note with appreciation that the instant application is granted the benefit of priority for the U.S. provisional Applications 60/115,435, filed on January 6, 1000, and 60/118,848, filed on February 5, 1999.

The Examiner, however, alleged that the sequence of ORF 8, as described on pages 71-72 of 60/118,848 is note the same as the sequence of ORF 8 in the instant specification and requested clarification of this alleged discrepancy. The Examiner, however, further noted that 60/118,848 does correctly disclose the same primer pairs for ORF 8 as found inconstant Table II.

Review of page 71 of the 60/118,848 priority document shows that the term "orf8 →" appears to have printed out of position. The correct sequence for ORF8 is given on this page beginning at nucleotide 58105. Closer examination will reveal that the correct start codon (ATG) is underlined. In addition, there is a wider space between the 58101 line and the 58051 line indicating

that applicants recognized the location of this codon and the wide line spacing was, presumably, to accommodate the "orf8 →" designation. Given that Applicants were clearly in possession of the correct ORF8 sequence (as evidenced by page 71) and correct primers to uniquely identify and amplify this open reading frame, Applicants were clearly in possession of the claimed invention. Consequently Applicants are entitled to the priority date of the 60/118,848 application.

Information Disclosure Statement.

The Examiner noted that reference AP was not considered because this reference was allegedly omitted. In addition, the Examiner noted that Reference AK (Debabov *et al.*) was not considered because the citation was incomplete (although the reference was cited).

Applicants enclose herewith an additional Form 1449 correcting the citation for AK. The requested reference (Debabov *et al.*) is on order and will be furnished shortly. Applicants believe no additional fees are required for this submission, because both references were identified in the previously submitted Information Disclosure Statement.

Drawings.

The drawings were considered informal for the reasons detailed in the PTO Form 948. Formal drawings are provided with this amendment.

Sequence Listing Rules.

The Examiner indicated that the application is not in compliance with sequence rules, 37 C.F.R. §§ 1.821-1.825. In particular, the Examiner alleged that the description of Figure 8C does not particularly point out which SEQ ID NO is the nucleotide sequence disclosed and which is the amino acid sequence disclosed. The description of Figure 8C has been amended to provide the required description thereby obviating this rejection.

The Examiner further alleged that the sequence listing is confusing because the references to various accession numbers and the division of the entire gene cluster between SEQ ID NOs: 1 and 2. Applicants note that the sequence listing is presently in compliance with 37 C.F.R. §1.821 through §1.825. Moreover, the sequences of each of the recited ORFs is provided and these ORFs are clearly identified in the present sequence listing. Accordingly, in view of the cost of revising the sequence listing and Applicant's belief that the sequence listing presently is in compliance with the rules, the sequence listing is not revised herein.

Objections to the Specification.

The specification was objected to for being allegedly confusing for the reasons described below:.

A) Figure 6.

The Examiner alleged that in the description of Figure 6, Figures 6A-6F must be described separately. The Figure 6 legend (page 15, lines 13-15) has been amended to provide the requested description thereby obviating this rejection. Support for this amendment is found in Figure 6 as originally filed.

B) Figure 9.

The Examiner alleged that Figure 9 mentions underlining that is not found in the Figure itself. The Figure 9 legend is amended herein to omit reference to the underlining thereby obviating this rejection.

C) Figure 11.

The Examiner alleged that in the description of Figure 11, Figures 11A-11D must be described separately. The Figure 11 legend (page 16, lines 1-1) has been amended to provide the requested description thereby obviating this rejection. Support for this amendment is found in Figure 11 as originally filed.

D) Page 19, line 14:

The Examiner alleged that the accession numbers on page 19, line 14 (AT-149091 and AT-210249) are unclear because they could not be identified in GenBank and because three accession numbers reference two SEQ ID NOs. Applicants note that "AT-149091" should have been "AF149091" and that AT-210249 should have been "AF210249". The "AT" was a typographical error which could readily be inferred from the correct ID "AF210311" listed in the same line, from the correct accession number given on page 15, lines 18-24. The Accession numbers could also readily be determined using the NCBI Entrez browser and searching for " streptomyces and bleomycin and biosynthetic" or other similar searches. Accordingly the corrections do not introduce new matter and the Accession numbers are corrected with entry of this amendment.

With respect to the three accession numbers, it is noted that GenBank states that "Accession AF210249 replaces sequence(s) AF149091". The AF210311 listing pertains specifically to the *Streptomyces verticillus* phosphopantetheinyl transferase (PptA) gene.

E) Table I, page 19.

The Examiner indicated the SEQ ID NOS would be helpful in Table 1 on page 19. Applicants note that SEQ ID Numbers are not required by the rules. Moreover, as certain Blm's correspond to several SEQ ID Numbers (see , *e.g.* Figures 1B and 2) Applicants believe insertion of such SEQ ID Numbers would result in unnecessary confusion.

F) Table 1 accession number.

The Examiner alleged that the accession number "AA07904.1" is unclear and cannot be identified in GenBank. Applicants have deleted *this* accession number with entry of this amendment thereby obviating this rejection.

G) Table II, position reference is unclear.

The Examiner alleged that the "position" reference in Table II is unclear since the gene cluster is apparently divided between SEQ ID NOs: 1 and 2. Applicants note that the position references are given with respect to the gene cluster, e.g. as delineated in Figures 1B and 2. Accordingly, the position reference is sufficiently clear and this objection should be withdrawn.

H) Page 47, line 19 reference to "(18)".

The Examiner alleged that the reference to "(18)" on page 47, line 19 is unclear. This reference has been eliminated with entry of this amendment thereby obviating this rejection.

I) Page 69 accession numbers.

The Examiner alleged that the accession numbers "AL008967", AL031107", and "AL049863" listed on page 69 are unclear and cannot be found in GenBank. Applicants have performed a search of the nucleotide database with the NCBI Entrez browser and identified all three accession numbers as follows:

AL008967
Mycobacterium tuberculosis H37Rv complete genome; segment 122/162

gi|3261491|emb|AL008967.1|MTV002[3261491]

AL031107
Streptomyces coelicolor cosmid 5A7
gi|20520753|emb|AL031107.2|SC5A7[20520753]

AL008769
Drosophila melanogaster STS determined from European Mapping Project cosmid, sequence tagged site
gi|2598296|emb|AL008769.1|DM107F9S[2598296]

All three accession numbers are available in GenBank using a routine search. Accordingly, the Examiner should withdraw this objection.

J) Page 70, line 29.

The Examiner alleged that the reference to "(FIGURE)" on page 70, line 29 is unclear. This reference has been eliminated with entry of this amendment thereby obviating this rejection.

Claim Objections.

Claims 1-21, 23, 40-45, 65-66, 68-69, and 71-73 were objected to for containing non-elected subject matter as follows:

A) Claims 1-5.

Claims 1-5 (independent claim 1) were objected to as being drawn to nucleic acid sequences of any one of ORFs 8-41, while only ORF 8 is elected. Claim 1 has been amended herein to recite ORF8 thereby obviating this objection.

B) Claims 6-8.

Claims 6-8 (independent claim 6) were objected to as being drawn to nucleic acid sequences that encode NRPs that are wholly distinct from the nucleic acid sequence encoding the oxidase that is ORF 8. Claims 6-8 are cancelled with entry of this amendment thereby obviating this rejection. This amendment is made without prejudice and is not to be construed as abandonment of the previously claimed subject matter or agreement with the Examiner's position

C) Claims 9-15.

Claims 9-15 (independent claim 9) were objected to as being drawn to nucleic acid sequences encoding any protein from the BLM gene cluster, while only ORF 8 is elected. Independent claim 9 is amended herein to expressly recite "an isolated nucleic acid comprising a nucleic acid encoding a protein comprising the sequence of SEQ ID NO:115" thereby obviating this objection.

D) Claims 16-18

Claims 16-18 9independent claim 16) were objected to as being drawn to nucleic acid sequences hybridizing to any ORF listed, while only ORF 8 is elected. Claims 16-18 are cancelled with entry of this amendment, while claim 17 is amended to depend from claim 9 thereby obviating this objection. This amendment is made without prejudice and is not to be construed as abandonment of the previously claimed subject matter or agreement with the Examiner's position

E) Claims 19-20

Claims 19-20 (independent claim 20) are objected to as being drawn to nucleic acid sequences that are variants of any ORF listed, while only ORF 8 is elected. Claims 19-20 are cancelled with entry of this amendment thereby obviating this objection. This amendment is made without prejudice and is not to be construed as abandonment of the previously claimed subject matter or agreement with the Examiner's position.

F) Claims 21 and 23.

Claims 21 and 23 contain no specific reference to OFF8, however the claims are being examined as if the nucleic acid sequences claimed must contain ORF 8. As claim 21 is directed to "a gene cluster comprising open reading frames encoding polypeptides sufficient to direct the assembly of a bleomycin" Applicants agree that such a gene cluster can comprise ORF8..

G) Claims 40-45.

Claims 40-45 were objected to as claiming non-elected subject matter as noted for claims 1-21 and 23. In view of the amendments described herein, claims 40-45 no longer claim non-elected subject matter.

H) Claims 65-66 and 68-69.

Claims 65-66, and 68-69 allegedly claim or are related to nucleic acid sequences that are not ORF 8 and are not treated further on their merits as non-elected inventions. Claims 65-66, and 68-69 are cancelled with entry of this amendment. This amendment is made without prejudice and is not to be construed as abandonment of the previously claimed subject matter or agreement with the Examiner's position.

I) Claims 71-73.

Applicants note that claims 71-73 contain no specific reference to ORF 8, but are being examined as if the cells claimed must contain a modified ORF 8.

Office Action Item 12:

Claim 72 was objected to for containing a typographical error. Claim 72 is amended herein to correct "bene" to "gene" thereby obviating this rejection.

Office action Item 13.

Claim 42 was objected to under 37 C.F.R. §1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claim 42, as amended herein depends from claim 40, which ultimately incorporates any one of claims 1, 2, 3, 5, 9, 10, 12, 13, 14, 15, 17, and 21. Claim 42 does further limit the subject matter of a previous claim and is of proper dependent form. Accordingly, this objection should be withdrawn.

35 U.S.C. §112, Second Paragraph.

Office action Item 14.

Claims 1-5, 9-20, 23, 40-45, and 71-73 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because of the use of the term "nucleic acid". According to the Examiner, "nucleic acids are small molecules, while linear sequences of nucleic acids encoding proteins are useful biological tools. Applicants respectfully traverse.

The Examiner is simply incorrect in her understanding of the definition of "nucleic acid". As defined by the Biotech Life Science Dictionary: (http://biotech.icmb.utexas.edu/search/dict-search.phtml?title=nucleic+acid) a nucleic acid is "[a] **large molecule composed of nucleotide**

subunits." Similarly, General Chemistry Online (http://antoine.frostburg.edu/chem/senese/101/glossary/n.shtml#nucleic%20acid) defines a nucleic acid as: "A polymer made of repeating nucleotides . Examples are DNA and RNA.". Finally, it is noted that Lehninger (19750 Biochemistry, Second Ed., at page 318 states that "Deoxyribo**nucleic acid** (DNA) consists of covalently linked chains of deoxyribonucleotides, and ribo**nucleic acid** (RNA) consists of chains of ribonucleotides." [emphasis added]

Contrary to the Examiner's assertion, the term "nucleic acid" is used correctly to refer to macromolecules comprising nucleotide subunits. Accordingly this rejection should be withdrawn. Consistent with general usage, Applicants view the terms polynucleotide and nucleic acid as equivalent. If the Examiner prefers the former term, she is hereby authorized to amend the claims by Examiner's amendment to refer to polynucleotides rather than to nucleic acids.

Office Action Item 15.

Claims 1-5, and 40-45 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because the structure/indentations of claim 1 are allegedly unclear by the use of tab formation. The claims are amended herein to eliminate the tab indentations thereby obviating this rejection.

Office Action Item 16.

Claims 1-5, and 40-45 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because the term "encoding" in claim 1, line 3 was allegedly unclear. Claim 1 is amended herein to recite "An isolated nucleic acid comprising a polynucleotide that hybridizes under stringent conditions to a SEQ ID NO:1, base pairs 57583-58854, wherein said polynucleotide encodes a protein that has an oxidase activity." It is clear that the term "encoding" refers to a DNA-protein relationship. Accordingly this rejection under 35 U.S.C. §112, second paragraph, should be withdrawn.

Office Action Item 17.

Claims 1-5, 10-20, and 40-45 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because the claims allegedly reference a sequence that is ORF 8 without referring

to specific SQ ID NOs. The claims are amended therein to recite SEQ ID NOs where appropriate thereby obviating this rejection.

Office Action Item 18.

Claims 1-5, and 40-45 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because "it is unclear how "'the nucleic acid of a bleomycin-producing organism" can be used as a template since, as noted above, nucleic acids are small molecules, while linear sequences of nucleic acids encode proteins are useful molecular biological tools. Applicants respectfully traverse.

As indicated above, the Examiner has confused the term "nucleic acid" with the term "nucleotide". As commonly defined, for example in the Medicinal Chemistry Dictionary (http://www.chem.qmw.ac.uk/iupac/medchem/ix.html#n5): " A nucleic acid is a macromolecule composed of linear sequences of nucleotides that perform several functions in living cells, e.g., the storage of genetic information and its transfer from one generation to the next DNA (deoxyribonucleic acid), the expression of this information in protein synthesis (mRNA, tRNA) and may act as functional components of subcellular units such as ribosomes (rRNA)." Accordingly, a nucleic acid can readily be used as a template and this rejection under 35 U.S.C. §112, second paragraph, is improper and should be withdrawn.

Office Action Item 19.

Claims 2-5, 10-15, and 40-45 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because the term "said nucleic acid" allegedly has unclear antecedent basis. Applicants have amended the claims to recite "[a]n isolated nucleic acid comprising a polynucleotide . . . " per the Examiner's recommendation. Accordingly, this rejection under 35 U.S.C. §112, second paragraph, is improper and should be withdrawn.

Office Action Item 20.

Claims 9-15, and 40-45 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because of the use of the phrase "a BLM gene cluster". Claim 9 is amended herein to recite " [a]n isolated nucleic acid comprising a nucleic acid encoding a protein comprising the sequence of SEQ ID NO:115." thereby obviating this rejection. This amendment is made without

prejudice and is not to be construed as abandonment of the previously claimed subject matter or agreement with the Examiner's position.

Office Action Item 21.

Claims 9-15, and 40-45 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because of the use of the phrase "a BLM gene cluster" without expressly defining BLM. Claim 9 is amended herein to recite " [a]n isolated nucleic acid comprising a nucleic acid encoding a protein comprising the sequence of SEQ ID NO:115." thereby obviating this rejection. This amendment is made without prejudice and is not to be construed as abandonment of the previously claimed subject matter or agreement with the Examiner's position.

Office Action Item 22.

Claims 16-18, and 40-45 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because the optional domains in claim 16 are allegedly varied while the elected ORF 8 is only disclosed as containing an oxidase domain. Claims 16 and 18 are cancelled herein, while claim 17 is now depended from claim 9 thereby obviating this rejection. This amendment is made without prejudice and is not to be construed as abandonment of the previously claimed subject matter or agreement with the Examiner's position.

Office Action Item 23.

Claims 16-18, and 40-45 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because the "actual '"ends"' of such domains, when described only vaguely by catalytic function or homologous function, is not definite." Applicants note that claims 16 and 18 are cancelled, herein, and claim 17 now depends from claim 9 thereby obviating this rejection. This amendment is made without prejudice and is not to be construed as abandonment of the previously claimed subject matter or agreement with the Examiner's position.

Office Action Item 24.

Claims 16-18, and 40-45 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because the term "stringent conditions" is allegedly unclear as to its metes and bounds. Applicants respectfully traverse.

Applicants note that claims 16 and 18 are cancelled, herein, however, the term "stringent conditions" now occurs in claim 1.

The Examiner is reminded that a claim is definite if "... read in light of the specification [it] reasonably apprise[s] those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits." *In re Jackson,* 217 USPQ. 804, 806 (BPAI, 1982).

The term "stringent conditions" is a term of widespread use in the field. Moreover the specification expressly defines stringent conditions as "about 5°C lower than the thermal melting point (T_m) for the specific sequence at a defined ionic strength and pH." (*see, e.g.,* page 10, lines 33-34). . One of skill in the art can readily determine stringent conditions for any nucleic acid in question (e.g., using any of a number of commercially available software programs such as DNAStar and the like).

The use of the term "stringent conditions" thus renders the claimed invention neither overbroad nor indefinite. The claims reasonably apprise one of skill in the art of the scope of the invention and are as precise as the subject matter permits. This rejection under 35 U.S.C. §112, second paragraph, is therefore improper and should be withdrawn.

Office Action Item 25.

Claims 21 and 40-45 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because the recitation of "a bleomycin" was allegedly unclear. Claim 21 is amended herein to recite "a bleomycin or a bleomycin analogue."

The term analogue as used in the context of "bleomycin " analogue is a term well understood by those of skill in the art. Chemicals and chemical analogues are commonly recognized and distinguished by those of ordinary skill in the art. In addition, Applicants note the term "analogue" is one frequently allowed by the Patent Office in various claims thus, for example: U.S. Patent 6,448,392 claims "[a] liponucleoside compound comprising an antiviral **nucleoside analogue**. . . ", U.S. Patent 5,962,532 claims ". . . b) injecting into the site **capsaicin or capsaicin analogue** in a dosage formulation having a concentration between about 0.01 and 10% by weight capsaicin. . . ", and U.S. Patent 6,232,346 claims ". . . the method comprising administering to a mammal an effective amount of a carrier and a nutritional supplement comprising L-Carnitine or its functional **analogue**,

Coenzyme Q10 (Ubiquinone) or its functional **analogue** and Taurine or a Taurine precursor in a single or divided daily dose."

The use of the term "bleomycin analogue" reasonably apprises one of skill in the art of the scope of the invention and is as precise as the subject matter permits. This rejection under 35 U.S.C. §112, second paragraph, should therefore be withdrawn.

Office Action Item 26.

Claims 40-45 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because claim 40 allegedly depended from claim 22 that is not a nucleic acid, but a polypeptide. Claim 40, as amended, now depends from any one of claims 1, 2, 3, 5, 9, 10, 12, 13, 14, 15, 17, and 21 all of which are directed to nucleic acids, thereby obviating this rejection.

Office Action Item 27.

Claims 72-73 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because the term "a resistance gene from the bleomycin gene cluster "is allegedly unclear. The term "a resistance gene from the bleomycin gene cluster is a term known to those of ordinary skill in the art. As stated in the specification,

> Davies and co-workers *previously* cloned **two BLM resistance genes (*blmA* and *blmB*)** from *Sv* ATCC15003 (Sugiyama *et al.* (1994) *Gene* 151: 11-16), and Calcutt and Schmidt (1994) *Gene*, 151: 17-21, sequenced a 7.2-kb DNA fragment flanking the *blmAB* genes, revealing seven open reading frames (orfs), none of which were found to encode Blm NRPS or PKS enzymes. [emphasis added] (page 46, line 29 - page 47, line 2).

Moreover, as stated in the note associated with Table 2:

> *ORF1* to ORF7 were reported by Schmidt (1994) *Gene* 151:17-21, who assigned ORF2 as *blmA* and ORF4 as *blmB*.

Finally, Applicants note that the reference to Table III has been eliminated. In view of this, Applicants submit that claims 72 and 73 meet the requirements of 35 U.S.C. §112, second paragraph and the rejection on these grounds should be withdrawn.

35 U.S.C. §112, First Paragraph, Description Requirement.

Office Action Item 28.

Claims 1-5, 16-18, and 40-45 were rejected under 35 U.S.C. §112, first paragraph, written description. In particular the examiner alleged that no relation between the claimed structure and the described function is in the claims.

Claim 1, as amended herein, now expressly recites:

> 1. An isolated nucleic acid comprising a polynucleotide that hybridizes under stringent conditions to a SEQ ID NO:1, base pairs 57583-58854, **wherein said polynucleotide encodes a protein that has an oxidase activity**. [emphasis added]

The claim as amended expressly provides a relation between the claimed structure and the described function. Accordingly, the rejection under 35 U.S.C. §112, first paragraph, on these grounds should be withdrawn.

Office Action Item 29.

Claims 9-15, 21, 23, 40-45, and 71-73 were rejected under 35 U.S.C. §112, first paragraph, written description. In particular the Examiner alleged that claims 9, 21, 23, and 71 are drawn to nucleic acid sequences claimed according to function alone. Applicants note that claim 9, as amended, is drawn to particular nucleic acids and does not recite function. Accordingly the rejection of claim 9 under 35 U.S.C. §112, first paragraph, written description should be withdrawn.

With respect to claims 21 and 71 (and respective dependent claims), the Examiner is reminded that "[t]he written description requirement does not require the applicant 'to describe exactly the subject matter claimed, [instead] the description must **clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed**. [emphasis added] '" *Union Oil Co. v Atlantic Richfield et al.* 208 F.3d 989 (Fed. Cir. 2000) *citing In re Gosteli*, 872 F.2d 1008, 1012, 10 U.S.P.Q.2D (BNA) 1614, 1618 (Fed. Cir. 1989).

In the instant case, claims 21 and 71 do not recite particular functions. Claim 21 is simply drawn to an isolated gene cluster encoding polypeptides sufficient to direct the assembly of a bleomycin or a bleomycin analogue, while claim 72 simply recites a cell comprising a modified

bleomycin gene cluster nucleic acid, said cell producing elevated amounts of bleomycin as compared to the wild type cell gene

Applicants have provided examples of an isolated bleomycin gene cluster, illustrations of modifications that can be made to the gene cluster to make bleomycin analogues (*see, e.g.,* pages 34, line 12-page 43, line 15), and a cell overexpressing bleomycin (*see, e.g.,* page 56, lines 1-18). One of skill, reading the specification would clearly recognize that Applicants have "**invented what is claimed**." Accordingly, the specification meets the requirements of 35 U.S.C. §112, first paragraph, written description and the rejection on these grounds should be withdrawn.

Office Action Item 30.

Claims 19 and 20 were rejected under 35 U.S.C. §112, first paragraph, written description. In particular the Examiner alleged that Applicants had not identified any particular representatives of the genus Blm gene cluster SNPs. Claims 19 and 20 are cancelled with entry of this amendment thereby obviating this rejection.

This amendment is made without prejudice and is not to be construed as abandonment of the previously claimed subject matter or agreement with the Examiner's position.

35 U.S.C. §112, first paragraph, scope of enablement.

Office Action Item 31.

Claims 1-5, 9-20, and 40-45 were rejected under 35 U.S.C. §112, first paragraph because the specification while enabling for nucleic acid sequences encoding proteins with the oxidase function described in the specification for ORF 8, allegedly does not reasonably provide enablement for nucleic acid sequences within the claims structural limitations, but having different functions.

Claim 1, as amended herein, recites:

> 1. An isolated nucleic acid comprising a polynucleotide that hybridizes under stringent conditions to a SEQ ID NO:1, base pairs 57583-58854, **wherein said polynucleotide encodes a protein that has an oxidase activity. [emphasis added]**

The claim as amended thus clearly recites an "oxidase activity" thereby obviating this rejection. This amendment is made without prejudice and is not to be construed as abandonment of the previously claimed subject matter or agreement with the Examiner's position.

Office Action Item 32.

Claims 21, 23, and 71-73 were rejected under 35 U.S.C. §112, first paragraph because the specification, while being enabling for nucleic acid sequences specifically disclosed in the specification, allegedly does not reasonable provide enablement of nucleic acid sequences describe according to function only. Applicants respectfully traverse.

The Examiner is respectfully reminded that to be enabling under §112, first paragraph, a patent must contain a description that enables one skilled in the art to make and use the claimed invention . **That some experimentation is necessary does not constitute a lack of enablement**; the amount of experimentation, however, must not be unduly extensive.

Whether undue experimentation is required by one skilled in the art is typically determined by reference to eight factors considered relevant to the inquiry: (1) quantity of experimentation necessary; (2) amount of guidance presented; (3) presence of working examples; (4) nature of the invention; (5) state of the prior art; (6) relative skill of those in the art; (7) predictability of the art; and (8) breadth of the claims. *In re Wands,* 8 USPQ2d 1400 (Fed. Cir. 1988) *citing Ex parte Forman Inc.,* 230 USPQ 546 (BPAI 1986).

Claim 21 is simply drawn to an isolated gene cluster encoding polypeptides sufficient to direct the assembly of a bleomycin or a bleomycin analogue, while claim 72 simply recites a cell comprising a modified bleomycin gene cluster nucleic acid, said cell producing elevated amounts of bleomycin as compared to the wild type cell gene.

The specification provides considerable guidance (Wands Factor 2) for the creation of such constructs (*see, e.g.,* pages 34, line 12-page 43, line 15) and additionally provides working examples (Wands Factor 3) (*see, e.g.,* page 56, lines 1-18). The nature of the invention is relatively straightforward being directed to PKS/NRPS pathways which are modular in nature and know to have interchangeable modules and/or domains. The state of the prior art is well developed (Wands Factor 5): PKSs and NRPSs are well known to those of skill in the art (see e.g.. background section). The level of skill of those in the art is high (Wands Factor 6), typically Ph.D. The predictability of the art is

good (Wands Factor 7), PKS pathways have been shown to have interchangeable modules and the same is true for NRPS pathways. The claims are relatively narrow (Wands Factor 8), pertaining specifically to bleomycin biosynthetic pathways. Finally, the only experimentation (Wands Factor I) required is at most, routine screening which, the Federal Circuit has already established does not amount to undue experimentation.

All of the factors recited in *In re Wands* indicate that performance of the claimed methods requires no undue experimentation. Accordingly, the rejection under 35 U.S.C. §112, first paragraph, should be withdrawn.

35 U.S.C. §102.

Office Action Item 33.

Claims 23, 40, 41, and 43-45 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by Schupp *et al.* (U.S. Patent 6,121,029). In particular, the Examiner alleged that Schupp *et al.* discloses an epothilone PKS gene cluster encoding PKSs and NRPs.

Claim 23, drawn to "[an isolated nucleic acid encoding a multi-functional protein complex comprising both a polyketide synthase (PKS) and a peptide synthetase (NRPS)." is canceled with entry of this amendment thereby obviating this rejection.

Office Action Item 34.

Claims 16, 17, 40, 41, and 43-45 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Redenbach *et al.* (1996) *Mol. Microbiol.*, 21(1): 77-96. The Examiner alleges that Redenback *et al.* teach a DA sequence that encodes a protein that is 34% identical to SEQ ID NO:115 and that such a sequence will hybridize to ORF 8 under stringent conditions. The Examiner is respectfully reminded that anticipation requires **all** of the limitations of a claim be found in the reference. *Kalman v Kimberly-Clark Corp.*, 218 USPQ 781, 789 (Fed. Cir. 1983).

Claim 1, as amended herein, recites

> 1. An isolated nucleic acid comprising a polynucleotide that hybridizes under stringent conditions to a SEQ ID NO:1, base pairs 57583-58854, **wherein said polynucleotide encodes a protein that has an oxidase activity**. [Emphasis added]

The Examiner has failed to establish that the referenced nucleic acid allegedly disclosed by Redenbach *et al.* encodes a protein that has an oxidase activity. The Examiner has therefore failed to make a *prima facie* case of anticipation and the rejection of claims 16, 17, 40, 41, and 43-45 under 35 U.S.C. §102(b) in light of Redenbach *et al.* should be withdrawn.

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 337-7871.

QUINE INTELLECTUAL PROPERTY LAW GROUP, P.C.
P.O. BOX 458
Alameda, CA 94501
Tel: 510 337-7871
Fax: 510 337-7877

Respectfully submitted,

Tom Hunter
Reg. No: 38,498

c:\toms work_amendments\407t uc ott\407t-895020us gene delivery\407t-895020us.am3.doc

APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE IN 09/477,962 WITH ENTRY OF THIS AMENDMENT

In the specification:

Page 15, lines 13-15:

Figures 6A-6F illustrate[s] the use of the *blm* NRPS and PKS enzymes to synthesize a variety of hybrid polyketide/peptide molecules including, but not limited to, a family of oxazolines/oxazoles, and thiazoline/thiazoles. **Figure 6A synthesis using BlmIX, BlmVIII, and BlmVII. Figure 6B synthesis using NRPS, BlmVIII, and BlmVII. Figure 6C synthesis using BlmIX, BlmVIII, and BlmVII. Figure 6D synthesis using BlmIX, BlmVIII, and NRPS (C, A^N, PCP). Figure 6E synthesis using BlmIX, BlmVIII, and NRPS (C, A^C, PCP, OX).**

Page 15, lines 18-24:

Figure 8A shows a restriction map of the *blm* gene cluster from *Sv* ATCC15003 (B, *Bam*HI). 8B shows the relative position of the *blmI*, *blmII*, and *blmXI* genes to the two *blmAB* resistance genes (blm^R, Blm resistance). Individual open reading frames are represented by open arrows. Figure 8C (SEQ ID NO:127 **nucleotide sequence and SEQ ID NO:128 amino acid sequence**[~~& 128~~]) shows the nucleotide sequence of the *blmI* gene. The potential ribosome-binding site (RBS) and the conserved motif for 4'-phosphopantetheinylation are underlined. The sequence has been deposited into GenBank under accession no. AF210249.

Page 15, lines 25-31:

Figure 9 shows an amino acid sequence comparison of BlmI (SEQ ID NO:133) with PCP domains of known type I NRPSs (Grs-2 [P14688] (SEQ ID NO:129), 36% identity, 58% similarity; Srfa-3 [Q08787] (SEQ ID NO:130), 40% identity, 64% similarity; Vir-s [Y11547] (SEQ ID NO:131), 36% identity, 60% similarity; Saf-b [U24657] (SEQ ID NO:132), 40% identity, 54% similarity). Given in brackets are nucleotide sequence accession numbers. The shaded letters indicate similar amino acids. Consensus residues are amino acids that are similar in more than three sequences. [~~The signature motif for 4'-phosphopantetheinylation is underlined.~~]

Page 16, lines 1-5:

Figures 11**A-11D** show[s] the enzyme architecture of type I and type II PKS and NRPS. A, adenylation domain; ACP, acyl carrier protein or ACP domain; AT, acyl transferase; C, condensation protein or C domain; KS, β-ketoacyl synthase domain; KSα, β-ketoacyl synthase α subunit; KSβ, β-ketoacyl synthase β subunit; PCP, peptidyl carrier protein or PCP domain. **Figure 11A illustrates a Type I PKS. Figure 11B illustrates a Type I NRPS. Figure 11C illustrates a Type II PKS. Figure 11D illustrates a Type II NRPS.**

Page 19, lines 12-19:

The nucleic acids comprising the *blm* gene cluster are identified in Tables I and II and listed in the sequence listing provided herein (SEQ ID NOS: 1 and 2, GenBank Accession numbers [AT-149091, AT-210249]**AF149091, AF210249**, AF210311). In particular, Table I identifies genes and functions of open reading frames (ORFs) responsible for the biosynthesis of the hybrid peptide/polyketide/peptide backbone and sugar moieties of bleomycin, while Table II identifies a number of ORFs comprising the *blm* gene cluster, identifies the activity of the catalytic domain encoded by the ORF and provides primers for the amplification and isolation of that orf.

Table 1 at pages 19-20:

Table I. Determined functions of ORFs in the bleomycin biosynthesis gene cluster

Gene	Amino acids	Sequence Homolog[1]	Proposed function[2, 3]
orf8	424	YqeR (BAA12461)	Oxidase
blmC	498	RfaE[~~(AA07904.1)~~]	NDP-glucose synthase
blmI	90	GrsB (P14688)	Type II PCP
blmD	545	NodU (Q53515	Carbamoyl transferase
blmE	390	RfaF (AAD16056)	Glycosyl transferase
orf13	187	MbtH (O05821)	Unknown
blmII	462	Nrp (CAA98937)	NRPS condensation enzyme
orf15	339	SyrP (1890776)	Regulation
blmII	935	HMWP2 (P48633), McbC (P23185)	A PCP Ox
blmIV	2626	HMWP2 (P48633)	C A PCP Cy A PCP Cy
orf18	638	AsnB (2293165)	Asparagine synthetase

blmF	494	RfbC (Q50864)/BlmOrf1 (507319)	Glycosyl transferase/β-hydroxylase
blmG	325	YtcB (2293288)	Sugar epimerase
blmV	645	McyB (2708278)	PCP C
blmVI	2675	ACoAS (1658531), PksD (S73014) SnbDE (CAA67249)	$\underline{A^4}$ $\underline{ACP}$ C A PCP C A
blmVII	1218	SyrE (3510629)	$\underline{C}$ A PCP
blmVIII	1841	HMWP1 (CAA73127)	$\underline{KS}$ AT $\underline{MT}$ KR $\underline{ACP}$
blmIX	1066	SafB (1171128)	C A PCP
blmX	2140	TycC (2623773)	C A PCP C A PCP
blmXI	688	SyrE (3510629)	NRPS condensation enzyme
orf28	239	SC9C7.04C (CAA22716)	Unknown
orf29	582	YvdB (CAB08068)	Transmembrane transporter
orf30	113	SmtB (P30340)	Regulation
orf31	117	PhnA (P16680)	Unknown

Page 47, lines 14-21:

Noteworthy are the genes encoding the putative NRPS and PKS enzymes. The *blmI, blmII,* and *blmXI* genes encode NRPSs with an unusual architecture. In contrast to all known NRPSs, which are of modular organization with each module consisting minimally of a condensation (C), an adenylation (A), and a peptidyl carrier protein (PCP) domain (1), BlmI, BlmII, and BlmXI are discrete proteins homologous to individual domains of type I NRPSs. We have characterized BlmI as a type II PCP[~~(18)~~]. The BlmII and BlmXI proteins could serve as candidates for type II condensation enzymes. It is unclear yet what role if any these discrete NRPS enzymes could play in BLM biosynthesis.

Page 70, line 22 - page 71, line 31:

In order to test if *pptA* actually encodes a functional PPTase, we decided to overproduce and purify the PptA protein, and assay its catalytic competence on putative substrate proteins or domains. The *pptA* coding sequence was amplified by PCR and cloned into the T5-promoter-based pQE-70 vector, yielding plasmid pQEPPT, in such a way that a hexahistidine tag would be added at the C-terminus of the protein. Expression of the pQEPPT construct in *E. coli* M15(pREP4) resulted in the overproduction of soluble His-tagged PptA which was readily purified by affinity chromatography on Ni-NTA agarose under non-denaturing conditions[~~(FIGURE)~~]. Because *pptA* belongs, by

sequence similarity, to the subfamily of PPTases involved in nonribosomal peptide synthesis, we first assayed its activity using two different apo-PCPs as protein substrates. The first one, BlmI, has been previously characterized in our laboratory as a discrete peptidyl carrier protein, or type II PCP, whose gene is found within the bleomycin-biosynthesis gene cluster of *S. verticillus* (Du et al. *Chem. Biol.* (1999) 6:507-517). For the second PCP substrate we used BlmX, a bimodular NRPS protein encoded in the same cluster (Fig. 2), as a source of a type I PCP, i. e. a PCP included in a multidomain NRPS. For the production of this type I PCP, we amplified by PCR a 1,898 bp fragment encoding the adenylation and PCP domains from the second module of BlmX. This DNA fragment was cloned into pMAL-c2x to yield pMAL1617, in which the type I PCP would be produced as a maltose-binding protein (MBP) fusion, MBlmX-2, with a predicted molecular mass of 108. 5 kDa. Introduction of pMAL1617 in *E. coli* TB1 resulted in good overproduction of MBlmX-2, about 40% soluble, which was purified by affinity chromatography using amylose resin. To test the PPTase activity, we incubated the purified PptA with BlmI and MBlmX-2 as putative protein substrates in the presence of (^{3}H)-(pantetheinyl)-CoASH, and the tritiated products were subjected to SDS electrophoresis and autoradiography. The well-characterized PPTase Sfp from *B. subtilis*, which exhibits a broad specificity for its protein substrate (Quadri et al. *Biochemistry* (1998) 37:1585-1595), was included as a positive control. In these experiments PptA exhibited a robust phosphopantetheinylation activity on both BlmI and MBlmX-2. Having demonstrated that PptA does in fact have PPTase activity on both type I and type II PCP substrates from nonribosomal peptide synthetases, we then proceeded to test two different acyl-carrier proteins (ACPs) as potential substrates. The first one, BlmVIII, is a monomodular multidomain polyketide synthase (PKS) which is encoded in the bleomycin-biosynthesis gene cluster of *S. verticillus* (Fig. 2). BlmVIII contains an ACP domain at its C-terminus, that is a type I ACP. For the second ACP substrate we used TcmM, a type II acyl carrier protein involved in the biosynthesis of the aromatic polyketide tetracenomycin C in *S. glaucescens* (Shen et al. *J. Bacteriol.* (1992) 174:3818-3821; Bao et al. *Biochemistry* (1998) 37: 8132-8138). For the production of TcmM, its coding sequence was transferred from a construct previously made in pET-22b (Gehring et al. *Chem. Biol.* (1997) 4:17-24) into the pET-28a vector to yield pET28a-TcmM, in such a way that a hexahistidine tag should be added at both the N-terminus and the C-terminus of the protein. Plasmid pET28a-TcmM was introduced into *E. coli* BL21(DE3), and TcmM was easily purified by affinity chromatography using Ni-NTA resin. In vitro phosphopantetheinylation assays were

performed as before, but using BlmVIII and TcmM as protein substrates, and PptA was able to posttranslationally modified both ACP substrates.

In the claims:

1. An isolated nucleic acid comprising a **polynucleotide that hybridizes under stringent conditions to a SEQ ID NO:1, base pairs 57583-58854, wherein said polynucleotide encodes a protein that has an oxidase activity.** [~~having the nucleic acid selected from the group consisting of~~

~~a nucleic acid encoding any one of Blm open reading frames (ORFs) 8 through 41;~~

~~a nucleic acid encoding a polypeptide encoded by any one of Blm open reading frames (ORFs) 8 through 41; and~~

~~a nucleic acid amplified by polymerase chain reaction (PCR) using any one of the primer pairs identified in Table II and the nucleic acid of a bleomycin-producing organism as a template.~~]

2. The isolated nucleic acid of claim 1, wherein said nucleic acid comprises a nucleic acid encoding at least **one additional open reading frame that encodes a polypeptide selected from the group consisting of SEQ ID NO:114, SEQ ID NO:113, SEQ ID NO:112, SEQ ID NO:111, SEQ ID NO:110, SEQ ID NO:109, SEQ ID NO:108, SEQ ID NO:107, SEQ ID NO:106, SEQ ID NO:105, SEQ ID NO:104, SEQ ID NO:103, SEQ ID NO:102, SEQ ID NO:101, SEQ ID NO:100, SEQ ID NO:99, SEQ ID NO:98, SEQ ID NO:97, SEQ ID NO:96, SEQ ID NO:95, SEQ ID NO:94, SEQ ID NO:93, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, and SEQ ID NO:126.** [~~two open reading frames selected from the group consisting of Blm open reading frames 8 through 41.~~]

3. The isolated nucleic acid of claim 1, wherein said nucleic acid comprises a nucleic acid encoding at least **two additional open reading frames encoding polypeptides independently selected from the group consisting of SEQ ID NO:114, SEQ ID NO:113, SEQ ID NO:112, SEQ ID NO:111, SEQ ID NO:110, SEQ ID NO:109, SEQ ID NO:108, SEQ ID NO:107, SEQ ID NO:106, SEQ ID NO:105, SEQ ID NO:104, SEQ ID NO:103, SEQ ID NO:102, SEQ ID NO:101, SEQ ID NO:100, SEQ ID NO:99, SEQ ID NO:98, SEQ ID NO:97, SEQ ID NO:96, SEQ ID NO:95, SEQ ID NO:94, SEQ ID NO:93, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, and SEQ ID NO:126.** [~~three open reading frames selected from the group consisting of Blm open reading frames 8 through 41.~~]

4. Cancelled.

5. The isolated nucleic acid of claim 1, wherein said **the sequence of said protein is SEQ ID NO:115.** nucleic acid comprises a nucleic acid encoding a protein encoded by a gene selected from the group consisting of blmI, blmII, and blmXI.

9. An isolated nucleic acid comprising a nucleic acid encoding a protein **comprising the sequence of SEQ ID NO:115. [~~encoded by a gene from a BLM gene cluster.~~]**

10. The nucleic acid of claim 9, wherein said nucleic acid **wherein the sequence of said protein is SEQ ID NO:115. [~~comprises a nucleic acid encoding a protein encoded by a gene selected from the group consisting of blmI, blmII, and blmXI.~~]**

11. Cancelled.

12. The nucleic acid of claim 9, wherein said nucleic acid **further** comprises a nucleic acid encoding a protein encoded by blmVIII.

13. The nucleic acid of claim 9, wherein said nucleic acid **further** comprises a nucleic acid selected from the group consisting of blmI, blmII, and blmXI.

14. The nucleic acid of claim 9, wherein said nucleic acid **further** comprises a nucleic acid selected from the group consisting of blmIII, blmIV, blmV, blmVI, blmVII, blmIX, and blmX.

15. The nucleic acid of claim 9, wherein said nucleic acid **further** comprises blmVIII.

17. The nucleic acid of claim **[16]9**, wherein said isolated nucleic acid comprises a nucleic acid encoding a module.

21. An isolated gene cluster comprising open reading frames encoding polypeptides sufficient to direct the assembly of a bleomycin **or a bleomycin analogue**.

40. An expression vector comprising a nucleic acid of any one of claims **1, 2, 3, 5, 9, 0, 12, 13, 14, 15,, 17, and 21.[~~through 23.~~]**

41. A host cell transformed with an expression vector of claim 40.

42. The host cell of claim 41, wherein said cell is transformed with an exogenous nucleic acid comprising a gene cluster encoding polypeptides sufficient to direct the assembly of a bleomycin or bleomycin analog.

43. The cell of claim 41, wherein said cell is a bacterial cell.

44. The cell of claim 43, wherein said cell is a Streptomyces cell.

45. The cell of claim 41, wherein said cell is a eukaryotic cell.

71. A cell comprising a modified bleomycin gene cluster nucleic acid, said cell producing elevated amounts of bleomycin as compared to the wild type cell.

72. The cell of claim 71, wherein said cell overexpresses a resistance gene from the bleomycin **[~~bene~~]gene** cluster.

73. The cell of claim 72, wherein said resistance gene is a **selected from the group consisting of blmA, and blmB.** **[~~gene listed in Table III.~~]**

APPENDIX B

CLAIMS PENDING IN USSN 09/477,962 WITH ENTRY OF THIS AMENDMENT

1. An isolated nucleic acid comprising a polynucleotide that hybridizes under stringent conditions to a SEQ ID NO:1, base pairs 57583-58854, wherein said polynucleotide encodes a protein that has an oxidase activity.

2. The isolated nucleic acid of claim 1, wherein said nucleic acid comprises a nucleic acid encoding at least one additional open reading frame that encodes a polypeptide selected from the group consisting of SEQ ID NO:114, SEQ ID NO:113, SEQ ID NO:112, SEQ ID NO:111, SEQ ID NO:110, SEQ ID NO:109, SEQ ID NO:108, SEQ ID NO:107, SEQ ID NO:106, SEQ ID NO:105, SEQ ID NO:104, SEQ ID NO:103, SEQ ID NO:102, SEQ ID NO:101, SEQ ID NO:100, SEQ ID NO:99, SEQ ID NO:98, SEQ ID NO:97, SEQ ID NO:96, SEQ ID NO:95, SEQ ID NO:94, SEQ ID NO:93, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, and SEQ ID NO:126.

3. The isolated nucleic acid of claim 1, wherein said nucleic acid comprises a nucleic acid encoding at least two additional open reading frames encoding polypeptides independently selected from the group consisting of SEQ ID NO:114, SEQ ID NO:113, SEQ ID NO:112, SEQ ID NO:111, SEQ ID NO:110, SEQ ID NO:109, SEQ ID NO:108, SEQ ID NO:107, SEQ ID NO:106, SEQ ID NO:105, SEQ ID NO:104, SEQ ID NO:103, SEQ ID NO:102, SEQ ID NO:101, SEQ ID NO:100, SEQ ID NO:99, SEQ ID NO:98, SEQ ID NO:97, SEQ ID NO:96, SEQ ID NO:95, SEQ ID NO:94, SEQ ID NO:93, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, and SEQ ID NO:126.

5. The isolated nucleic acid of claim 1, wherein said the sequence of said protein is SEQ ID NO:115. nucleic acid comprises a nucleic acid encoding a protein encoded by a gene selected from the group consisting of blmI, blmII, and blmXI.

9. An isolated nucleic acid comprising a nucleic acid encoding a protein comprising the sequence of SEQ ID NO:115.

10. The nucleic acid of claim 9, wherein said nucleic acid wherein the sequence of said protein is SEQ ID NO:115.

12. The nucleic acid of claim 9, wherein said nucleic acid further comprises a nucleic acid encoding a protein encoded by blmVIII.

13. The nucleic acid of claim 9, wherein said nucleic acid further comprises a nucleic acid selected from the group consisting of blmI, blmII, and blmXI.

14. The nucleic acid of claim 9, wherein said nucleic acid further comprises a nucleic acid selected from the group consisting of blmIII, blmIV, blmV, blmVI, blmVII, blmIX, and blmX.

15. The nucleic acid of claim 9, wherein said nucleic acid further comprises blmVIII.

17. The nucleic acid of claim 9, wherein said isolated nucleic acid comprises a nucleic acid encoding a module.

21. An isolated gene cluster comprising open reading frames encoding polypeptides sufficient to direct the assembly of a bleomycin or a bleomycin analogue.

40. An expression vector comprising a nucleic acid of any one of claims 1, 2, 3, 5, 9, 10, 12, 13, 14, 15, 17, and 21.

41. A host cell transformed with an expression vector of claim 40.

42. The host cell of claim 41, wherein said cell is transformed with an exogenous nucleic acid comprising a gene cluster encoding polypeptides sufficient to direct the assembly of a bleomycin or bleomycin analog.

43. The cell of claim 41, wherein said cell is a bacterial cell.

44. The cell of claim 43, wherein said cell is a Streptomyces cell.

45. The cell of claim 41, wherein said cell is a eukaryotic cell.

71. A cell comprising a modified bleomycin gene cluster nucleic acid, said cell producing elevated amounts of bleomycin as compared to the wild type cell.

72. The cell of claim 71, wherein said cell overexpresses a resistance gene from the bleomycin gene cluster.

73. The cell of claim 72, wherein said resistance gene is a selected from the group consisting of blmA, and blmB.